IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Kevy *et al.*	Atty. Dock No.:	1459.008A
Serial No.:	10/765,694	Group Art Unit:	1657
Filing Date:	January 27, 2004	Examiner:	Laura J. Schuberg
Title:	AUTOLOGOUS COAGULANT PRODUCED FROM WHOLE BLOOD	Confirmation No.:	1436

To: Commissioner for Patents[1]
P.O. Box 1450
Alexandria, VA 22313-1450

REPLY BRIEF UNDER 37 C.F.R §41.41

Dear Sir:

Appellants timely submit this Reply Brief in support of Appellants' appeal from the rejection of the claims by the Examiner in the final Office Action mailed April 26, 2010, and in response to the Examiner's Answer mailed April 26, 2011.

[1] CERTIFICATE OF TRANSMISSION
I hereby certify that this correspondence is being transmitted via EFS on June 22, 2011. /SF/

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I. STATUS OF CLAIMS

Status of the claims are unchanged from the Appeal Brief. Appellant appeals under 35 U.S.C. § 134(a) from a rejection of claims 1-18, 21 and 22. Claims 1-18, and 21 and 22 stand rejected and each of these rejected claims is being appealed. Claim 19 was canceled and claim 20 was withdrawn.

II. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

(1) Whether claims 1-3 and 7-15 are obvious under 35 U.S.C. §103(a) over Gray in view of Cochrum; and

(2) Whether claims 1-4, 7-18, 21 and 22 are obvious under 35 U.S.C. §103(a) over Coelho in view of Rock.

III. ARGUMENT

Applicants' arguments presented in the Appeal Brief on record are incorporated herein to the extent that they are not specifically addressed herein. For the sake of brevity, Applicants' remarks presented herein are for summary or clarification of comments presented in the Examiner's Answer.

A. GRAY IN VIEW OF COCHRUM

Claims 1-3, and 7-15 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Gray in view of Cochrum. Since claims 2-3 and 7-15 depend on claim 1, and since if a parent independent claim is nonobvious, then all dependent claims are nonobvious, Applicants focus on the Examiner's Answer in view of claim 1.

The present invention is directed to a method for the preparation of a stable autologous or homologous coagulant from whole blood. The direct precipitation of anticoagulated whole blood obviates the need for a plasma isolation step with unexpected results (*see* Appeal Brief). Here, claim 1 is directed to a method for the production of thrombin from anticoagulated whole blood, comprising: (a) obtaining a volume of anticoagulated whole blood from a subject; (b) mixing said anticoagulated whole blood with ethanol at room temperature; (c) incubating the mixture of b) at room temperature for a time sufficient to produce a cellular and specific plasma component precipitate and a supernatant; (d) separating the precipitate from the supernatant; and (e) recovering the supernatant wherein said supernatant contains a thrombin preparation comprising 80-90% of prothrombin-thrombin proteins, no detectable fibrinogen and 20-30% of baseline levels of anti-thrombin III (ATIII). Applicants position is that claim 1 is patentable over the two

obviousness rejections: (1) Gray in view of Cochrum, and (2) over Coelho in view of Rock.

Gray relates primarily to the advantage of using neutral salts that do not bind calcium as anticoagulants in the collection of whole blood as opposed to conventional use of calcium-binding anticoagulants. Gray teaches 1) the use of toxic levels of neutral salts as an anticoagulant for whole blood rather than conventional calcium-binding anticoagulants (for example, CPD, ACD or EDTA); and 2) consistent with what is known in the art, cryoprecipitation is performed on plasma, not whole blood. Contrary to the assertion made in the Examiner's Answer, Gray does not teach cryoprecipitation of whole blood without a plasma isolation step, nor is it exemplified.

Rather, Gray teaches a process for isolation of certain rare blood components by a cryoprecipitation step, that is, by freezing plasma to low temperature and then thawing at 0°C to 4°C. (see col. 4, lines 30-33). Moreover, one of skill in the art would recognize that cryoprecipitation is only ever performed on plasma and there is no apparent reason that one can glean from Gray for substituting a chemical method of precipitation (as in present invention) for cryoprecipitation (as in Gray), particularly where the starting material is whole blood.

Cochrum does not remedy the deficiencies of Gray. Like Gray, Cochrum relates to a method for obtaining purified isolated fibrinogen *from plasma*. In particular, Cochrum teaches that autologous fibrinogen is prepared from the patients own blood which is first separated into plasma, platelets and blood cells (*see* col. 10, lines 25-32 of Cochrum) *(i.e.* not using whole blood as in the present invention).

In Reply to the Examiner's Answer, Applicants' position is that this obviousness rejection under section 103(a) should be reversed because, *inter alia*, like Gray, Cochrum does not teach or

suggest 1) precipitation of whole blood; 2) precipitation with ethanol; and 3) the step of recovering a supernatant that contains a thrombin preparation comprising 80-90% of prothrombin-thrombin proteins, no detectable fibrinogen and 20-30% of baseline levels of anti-thrombin III (ATIII), as recited in claim 1. Thus, Cochrum does not teach or suggest, either alone or in combination with Gray, the method of producing thrombin as presently claimed. Accordingly, the claimed invention cannot be obvious over Gray in view of Cochrum.

Moreover, there is no teaching, suggestion, or motivation in the cited references or in the prior art that would have led one of ordinary skill to modify Gray's cryoprecipitation method or to combine such teaching with Cochrum's disclosure of a method for obtaining fibrinogen from plasma to arrive at the instantly claimed invention because, *inter alia*, the presently claimed invention includes the step of mixing whole blood with ethanol. Therefore, for at least this reason, Cochrum cannot compensate for the deficiencies in the teachings of Gray.

Whole blood (present invention) and plasma (prior art) represent distinctly different starting materials. As indicated in the Declaration of Dr. Sherwin Kevy (submitted as Exhibit 5 of Appeal Brief), in the event that the person of skill would even be motivated to use whole blood in the first place, he/she would have known that precipitation of an anticoagulated whole blood preparation would result in a preparation containing significant levels of cell debris and cellular proteins not present in a similarly processed plasma preparation. The skilled artisan would have been taught away from using whole blood to practice the presently claimed invention because use of whole blood would be associated with unwanted cell debris and cellular proteins.

As indicated in the declaration of the independent expert, Dr. Mandle from Harvard Medical School, a skilled artisan:

"would have known that precipitation of an anticoagulated whole blood preparation would result in a preparation containing significant levels of cell debris and undesirable cellular proteins not present in a similarly processed plasma preparation. One of skill in the art at this time would have believed that the presence of these proteins and other debris would be likely to degrade or otherwise interfere with the quality of attempted protein isolations, due to the higher chance of contamination in the form of undesired proteins being present in the final sample."

"At the time the application was filed, the standard of practice for the production of a thrombin preparation from human blood, as outlined by Dr. Kevy, consisted of taking a sample of anticoagulated whole blood and first removing the cells to obtain a plasma fraction."

"as late as 2005, the relevant art…taught only the use of plasma for the production of human thrombin (See Kumar et al. *Stability of human thrombin produced from 11 ml of plasma using the thrombin processing device.* J Extra Corpor Technol. 37:390-395 2005). Preparation of thrombin from whole blood, without a plasma isolation step, was not viewed in the art as desirable due to the presence of a significant amount of extraneous debris. In my opinion, the invention shows an unexpected result of using whole blood, in that the hemolysis that occurs during preparation of the sample may actually ***enhance*** the process in terms of reducing the time required for agglomeration and precipitation of inhibitor proteins, compared to using plasma as a starting material. This phenomenon is described in the invention disclosure, on page 4, and also in paragraph [0015] of the specification of the application as originally filed. However, I believe one of skill in the art at the time would have come to the opposite conclusion."

(*see* Declaration of Dr. Mandle, paragraphs 8-10).

Thus, according to Dr. Robert Mandle, the present invention shows an unexpected result of using whole blood, in that the hemolysis that occurs during preparation of the sample using the instantly taught method may actually enhance the process (*i.e.* do the opposite of what would have been expected by an ordinary skilled artisan).

For at least the reasons adumbrated above and in the Appeal Brief, claim 1 and its dependent claims 2-3 and 7-15 are not rendered obvious by Gray in view of Cochrum. Accordingly, reversal of the examiner's rejection under U.S.C. §103(a) as being unpatentable over Gray in view of Cochrum is respectfully requested.

B. COELHO IN VIEW OF ROCK

Since Rock was cited in the obviousness rejection only to demonstrate that the claimed anticoagulants are well known in the art (*see* page 21 of Examiner's Answer), Applicants focus on the primary Coelho reference and the Examiner's Answer. The Examiner's Answer contends that Coelho teaches precipitation of whole blood directly with ethanol. Applicants respectfully disagree. Coelho teaches

> "preparing a fraction enriched in prothrombin by use of Ethanol to substantially enhance the concentration of prothrombin and at the same time remove or denature naturally occurring ingredients within ***plasma***, such as Fibrinogen and Antithrombin III which can bind to, block, interfere with or inhibit prothrombin or its subsequent activation to long-term functional thrombin"
>
> (Coelho, col. 6, lines 27-33).

This statement clearly identifies the fraction in which prothrombin is enriched by use of ethanol as a plasma fraction. Consistent with the interpretation of the language in claim 17 "sequestering prothrombin from the whole blood by addition of ethanol," throughout the specification, Coelho refers to the sequestration of prothrombin and subsequent derivation of autologous thrombin from plasma, not from whole blood (abstract; col. 6, lines 27-30; col. 6, lines 44-47; col. 7, lines 10-16; col. 7, lines 38-40; col. 9, lines 13-17). Notably, nowhere does Coelho, in claim 17 or anywhere else, disclose that ethanol is added to or mixed "with whole blood." Rather, Coelho in

claim 17, states the "addition of ethanol" but neglects to specify to what ethanol is added. However, the Coelho specification clearly discloses that ethanol is added to plasma, not whole blood.

The Examiner's Answer on page 19 argues that Coelho "specifically states that the blood product used is preferred to be plasma (column 9, lines 13-15) which requires that other blood products, while less preferred, are also acceptable." According to this section of Coelho:

> "Since it is preferred that the blood product admitted to the inlet 2 be plasma, the whole blood is first processed either by filtering, centrifugation, or another means of settling to remove the heavier red blood cells from the blood products, leaving plasma therebeyond for use in the FIG. 1 device."
>
> (Coelho, Col. 9, lines 13-17)

Thus, Coelho refers to the sequestration of prothrombin and subsequent derivation of autologous thrombin *from plasma*, not from whole blood (*see* Coelho abstract; col. 6, lines 27-30; col. 6, lines 44-47; col. 7, lines 10-16; col. 7, lines 38-40; *col. 9, lines 13-17*).

Likewise, the description of Coelho's device for obtaining the thrombin repeatedly refers to plasma and not to whole blood (col. 9, lines 7-10, lines 36-38, lines 47-50 etc.). The Examiner's Answer also relies on claims 17, 55, 97, 99, 107 and 112 for the position that thrombin is isolated from whole blood. Yet, each of these claims recite in one form or another a method for extracting autologous thrombin from a patient by obtaining whole blood from a person; sequestering plasma from the whole blood; converting the prothrombin to thrombin; loading the thrombin into a syringe and using the syringe to dispense the thrombin to stem blood

flow (*see* for e.g. claim 17 of Coelho reproduced *infra*).[2] Nowhere, however, do any of these claims recite mixing whole blood with ethanol. Rather, the claims fail to teach or suggest the mixing of ethanol "with whole blood." Both Coelho's claims and Coelho's specification specifically teach preparation of "a fraction enriched in prothrombin by use of ethanol to substantially enhance the concentration or prothrombin ...within plasma", not whole blood.

Coelho clearly discloses that ethanol is added to plasma, not whole blood (*see* all examples provided on pages 18-21 of Appeal Brief). Coelho fails to provide any evidence from which one of skill in the art would conclude that precipitation of whole blood was either desirable or advantageous for the preparation of thrombin as presently claimed. Furthermore, even if claim 17 could be read as teaching addition of ethanol to whole blood, which it does not, it is Applicants' position that the specification of Coelho contains no suggestion or guidance from which one of skill in the art, using his/her own knowledge of whole blood fractionation, would conclude that whole blood and plasma are interchangeable for use in the Coelho method.

Applicants suggest that Coelho's specification as filed was not intended to encompass claims to a method of extracting thrombin from whole blood. The numerous references in the specification to plasma suggest that only the plasma embodiment was contemplated at the time the application was filed. The Examiner's Answer refers to claim 17, however, this claim was not in the specification of Coelho as originally filed. Indeed and solely for the sake of argument, even if claim 17 where to be construed as the Examiner contends, the claim is not supported in

[2] Claim 17 recites: a method for extracting and then dispensing thrombin, the steps consisting of: taking whole blood from a person, sequestering prothrombin from the whole blood by addition of ethanol, wherein ethanol is present at a concentration between about 8% and about 20% volume per unit volume, converting the prothrombin to thrombin, loading the thrombin into a syringe, and using the syringe to dispense the thrombin to stem blood flow. Applicants suggest that the specification as filed was not intended to encompass claims to a method of extracting thrombin from whole blood. The numerous references in the specification to plasma suggest that only the plasma embodiment was contemplated at the time the application was filed.

any form by Coelho's own specification and as such claim 17 violates the rule that new matter cannot be added to a claim during prosecution of an application.

Furthermore, claim 17 of Coelho does not recite a step for removing the inevitable precipitate of cell debris and cellular protein components that result from mixing ethanol with whole blood, a phenomenon that does not occur with plasma (Coelho uses plasma) since the blood's cellular component has already been removed (*see* footnote 2). Coelho's disclosure of a method of extracting thrombin from whole blood without a precipitate removal step is, at best, inconsistent with the teachings of the specification discussed above. According to Coelho, the purpose of the step of adding ethanol is to enrich prothrombin in the plasma and at the same time, for example, remove fibrinogen from the prothrombin.

Coelho's specification, while it contains ample guidance with respect to the method of using plasma as a starting material, is silent as to any additional considerations taking into account the significant differences between plasma and whole blood. The skilled artisan would recognize that whole blood and plasma represent completely different starting materials.

The Examiner's Answer states that there are two reasons why Applicant's position is unpersuasive regarding Coelho's addition of ethanol to whole blood. First, it is alleged it is because Coelho's claims are directed to a method for extracting and then dispensing thrombin, the steps consisting of: taking whole blood from a person, sequestering prothrombin from the whole blood by addition of ethanol etc… The Examiner's Answer contends that since the transitional phrase "consisting of" is used, it does not allow for additional steps such as sequestering of plasma, and as such, the skilled artisan would add ethanol to whole blood.

In response, Applicants respectfully note that having not found any express teaching or suggestion anywhere in Coelho that ethanol is added to whole blood, the Examiner's Answer here is implying what is not there. The argument is in effect an inherency argument, and inherency has no place in an obviousness rejection. In re Spormann, 150 USPQ 449, 452 (CCPA 1966). The argument that it is implicit that a skilled artisan would add ethanol to whole blood in view of Coelho's claims is ill founded, especially so because the text of Coelho's own specification on more than a dozen times indicates otherwise (*see* above and Appeal Brief). Moreover, a skilled artisan would have recognized the problems of using whole blood and would have been taught away from practicing the presently claimed invention (*see* for example §1.132 Declaration of Dr. Mandle of Harvard Medical School; *see* also the evidence on record of surprising results and teaching away (for *e.g.* on page 24-26 of Appeal Brief); *see* also supporting literature submitted with the Appeal Brief).

The Examiner's Answer's other (second) reason why Applicant's position is unpersuasive regarding Coelho's addition of ethanol to whole blood is that "the establishment of a preferred blood product necessarily establishes that another blood product is a less preferred alternative." (*see* page 19 of Examiner's Answer). Again, the Examiner's Answer has ignored the express teachings of Coelho, the level of skill in the art at the time, the problems associated and reported with use of whole blood, and the surprising result found by the present inventors. Rather, the Examiner's Answer appears to make another inherency argument. Applicants note that subject matter is inherent when extrinsic evidence makes it clear that the subject matter necessarily flows from a disclosure of cited art. (*MPEP* 2112). That is, the Examiner's other main position is that since Coelho said X is preferred, even if Coelho does not teach or suggest Y, there must be a Y because Coelho did not limit itself to X and only said that X is "preferred."

Separately, the Examiner's Answer discounts the two 37 CFR §1.132 Declarations on file, contending instead that Coelho is patented and is enabled with respect to the addition of ethanol to whole blood. Having addressed the merits of Coelho *infra* and in the Appeal Brief, from a procedural perspective, Applicants respectfully are aware that an Examiner is allowed to be unpersuaded by evidence presented by an Applicant. However, evidence, such as in the form of a §1.132 declaration, must nonetheless be given proper consideration. For example, BPAI has consistently reversed decisions based on Examiner failing to properly consider the submitted evidence. For example, in Ex parte Malone (Appeal 2009-003894), the BPAI took issue with the Examiner for a "largely dismissive" response to the Applicants' § 1.132 declaration which presented evidence of non-obviousness.

Here, the examiner ignores the text of Coelho's own specification which is in direct conflict with the examiner's interpretation, the fact that a skilled artisan would have recognized the problems of using whole blood and would have been taught away from practicing the presently claimed invention, Coelho's teaching away of using whole blood (Coelho uses plasma), and the inventors' surprising results (*see* for example §1.132 declaration of Dr. Mandle, page 5 of this paper). Instead, the examiner contends that although Applicants show and argue the unexpected use of whole blood for producing thrombin, this is insufficient because "this step is expressly claimed in the Coelho patent." Applicants respectfully disagree for reasons outlined *infra* and in more detail in the Appeal Brief.

On a final note, the Examiner's Answer also cites Xiao *et al.* and Gray *et al.*, contending both were cited in prior and current rejections. Demopoulos *et al.*, Weissbach *et al.*, and Meucci *et al.* are also cited on page 21 of the Examiner's Answer. The examiner uses these five cited

references, alleging that fractionation of whole blood by precipitation is a known alternative. Xiao was previously cited in a formal rejection and was overcome. Gray is discussed above. Applicants note that Demopoulos, Weissbach, or Meucci are mentioned in the Examiner's Answer, however, neither of these references have ever been cited in a formal rejection in an Office Action. Applicants respectfully will spare comment on these references since there is no rejection based upon them to respond to. There have been many Office Actions during prosecution of the instant application and ample opportunity for the examiner to formally use these references in a specific rejection, noting that these references were first mentioned (but not used in a rejection) more than two years ago. In any event, Applicants do not believe these three references are pertinent to the patentability of the instant claims.

For at least the reasons adumbrated above and in the Appeal Brief, claim 1 and its dependent claims 2-4 and 7-18, and independent claim 22 and its dependent claim are not rendered obvious by Coelho in view of Rock. Accordingly, reversal of the examiner's rejection under U.S.C. §103(a) as being unpatentable over Coelho in view of Rock is respectfully requested.

C. OBVIOUSNESS AND INHERENCY

In the context of rejecting claims 1-3, and 7-15 under 35 U.S.C. §103(a) as being unpatentable over Gray in view of Cochrum, and rejecting claims 1-4, 7-18 and 21-22 under 35 U.S.C. §103(a) as being unpatentable over Coelho in view of Rock, the Office Action contends that certain claim limitations of claim 1 are descriptions of the thrombin product using the obvious steps of the instant application and are therefore the inherent result of following those steps.

The present invention includes the step of recovering a thrombin preparation comprising (1) 80-90% of prothrombin-thrombin proteins, (2) no detectable fibrinogen and (3) 20-30% of baseline levels of anti-thrombin III (ATIII), as is recited in claim 1. Neither Gray, Cochrum, Coelho or Rock teach such a product, nor can one claim that the autologous thrombin of the prior art inherently meets these criteria given the lack of specifics provided by the cited prior art for preparation of thrombin using whole blood. The method practiced will determine the properties of the product.

For example, one of skill in the art would have recognized that for producing thrombin from blood, the precipitation of an anticoagulated whole blood preparation would result in a preparation containing significant levels of cell debris and cellular proteins not present in a similarly processed plasma preparation and therefore, would likely require different handling from plasma. As such, a person of ordinary skill would not even be motivated to use whole blood in the first place (see claim 1), given its associated problems. Moreover, Applicants respectfully point out that the principle of inherency has no place in the determination of obviousness under 35 USC Section 103. In re Spormann, 150 USPQ 449, 452 (CCPA 1966).

In sum, Applicants respectfully first point out that the principle of inherency has no place in the determination of obviousness under 35 USC Section 103, and second that even if one were to ignore this law, the method of the present invention for producing thrombin is not obvious or inherent.

IV. CONCLUSION

Applicants respectfully request that the examiner's rejection of independent claim 1 under 35 U.S.C. §103(a) as being unpatentable over Gray in view of Cochrum, and independent claims 1 and 22 under 35 U.S.C. §103(a) as being unpatentable over Coelho in view of Rock be reversed. Since there are two independent claims on appeal (claims 1 and 22), Applicants respectfully contend that should the Board decide claims 1 and 22 are non-obvious, pending dependent claims should also be found to be non-obvious. The Board of Patent Appeals and Interferences is respectfully requested to overturn the two obviousness rejections and to remand the application to the Examiner for allowance.

Respectfully submitted,

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Date: June 22, 2011

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